

# An international Delphi consensus regarding best practice recommendations for hyperkalaemia across the cardiorenal spectrum

James O. Burton<sup>1\*</sup>, Andrew J.S. Coats<sup>2</sup>, Csaba P. Kovesdy<sup>3</sup>, Biff F. Palmer<sup>4</sup>, Ileana L. Piña<sup>5</sup>, Giuseppe Rosano<sup>6</sup>, Manish M. Sood<sup>7</sup>, and Shelley Zieroth<sup>8</sup>

<sup>1</sup>Department of Cardiovascular Sciences, University of Leicester, Leicester, UK; <sup>2</sup>Monash University, Australia and the University of Warwick, Warwick, UK; <sup>3</sup>University of Tennessee Health Science Center, Memphis, TN, USA; <sup>4</sup>University of Texas Southwestern Medical Center, Dallas, TX, USA; <sup>5</sup>Central Michigan University, Mount Pleasant, MI, USA; <sup>6</sup>IRCCS San Raffaele Roma, Rome, Italy; <sup>7</sup>Ottawa Hospital Research Institute, University of Ottawa, Ottawa, Ontario, Canada; and <sup>8</sup>University of Manitoba, Winnipeg, Manitoba, Canada

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## Aims

Renin–angiotensin–aldosterone system inhibitors (RAASi) are guideline-recommended therapy for individuals with cardiorenal disease. They are associated with increased risk of hyperkalaemia, a common and life-threatening disorder for this population. RAASi-induced hyperkalaemia often leads to dose reduction or discontinuation, reducing cardiorenal protection. Guideline recommendations differ between specialties for the clinical management of hyperkalaemia. Using a modified Delphi method, we developed consensus recommendations for optimal management of hyperkalaemia in adults with cardiorenal disease.

## Methods and results

An international steering group of cardiologists and nephrologists developed 39 statements regarding hyperkalaemia care, including risk factors and risk stratification, prevention, correction, and cross-specialty coordination. Consensus was determined by agreement on an online questionnaire administered to cardiorenal specialists across Europe and North America. The threshold for consensus agreement was established a priori by the steering group at 67%. Across November 2021, 520 responses were received from Canada ( $n = 50$ ), France ( $n = 50$ ), Germany ( $n = 54$ ), Italy ( $n = 58$ ), Spain ( $n = 57$ ), the UK ( $n = 49$ ), and the US ( $n = 202$ ); 268 from cardiologists and 252 from nephrologists. Twenty-nine statements attained very high agreement ( $\geq 90\%$ ) and 10 attained high agreement ( $\geq 67\% - < 90\%$ ), with strong alignment between cardiologists and nephrologists.

## Conclusion

A high degree of consensus regarding hyperkalaemia evaluation and management exists among healthcare professionals. Based on high levels of agreement, the steering group derived six key recommendations for hyperkalaemia prevention and management in people with cardiorenal disease. Future studies examining the quality of hyperkalaemia care delivery are required.

## Keywords

Delphi method • Hyperkalaemia • Cardiorenal patients • Renin–angiotensin–aldosterone system inhibitors • Consensus recommendation • Novel potassium binder

\*Corresponding author. Department of Cardiovascular Sciences, University of Leicester, Glenfield General Hospital, Groby Road, Leicester LE3 9QP UK. Tel: +44 116 2588043, Email: jb343@le.ac.uk

## Introduction

Hyperkalaemia is a potentially life-threatening medical condition of elevated blood potassium levels; 3.5–5.0 mEq/L is considered the normokalaemic range in adults, while instances of hyperkalaemia >5.5 mEq/L are more clearly associated with adverse clinical outcomes.<sup>1</sup> There is no universally accepted definition for hyperkalaemia severity. The European Society of Cardiology (ESC) guidelines recommend using a lower cut-off for mild (>5.0 mEq/L), moderate (>5.5 mEq/L), or severe (>6.0 mEq/L) hyperkalaemia, for closer monitoring of patients who may be at risk of hyperkalaemic complications.<sup>2</sup> Other guidelines, such as those endorsed by the UK Renal Association (UKRA), utilise a more stringent outcome-associated definition (mild: >5.5 mEq/L, moderate: >6.0 mEq/L, and severe: >6.5 mEq/L).<sup>3</sup> Most individuals with hyperkalaemia (particularly those with mild hyperkalaemia) are asymptomatic but when symptoms do occur, they tend to be non-specific. Untreated, severe hyperkalaemia can result in life-threatening cardiac arrhythmias, muscle weakness, paralysis, and mortality.<sup>4</sup>

Heart failure (HF) and chronic kidney disease (CKD) often coexist and contribute to poor outcomes. In adults with cardiorenal disease, concomitant HF and CKD increases the risk of hospitalization, need for intensive care or kidney replacement therapy, and mortality<sup>5</sup>; consequently, median survival in this population is around half that of people with HF alone.<sup>6</sup> Those with cardiorenal disease are also less likely to receive guideline-directed medical therapy for HF, possibly due to concerns about hypotension, worsening kidney function, and hyperkalaemia. This may lead to worse cardiovascular outcomes.<sup>5</sup>

Renin–angiotensin–aldosterone system inhibitors (RAASi) are an evidence-based treatment for many individuals with both HF and CKD to prevent or slow progression<sup>7</sup>; however, use of RAASi is also a risk factor for hyperkalaemia.<sup>3</sup> Cardiology- (ESC, the Canadian Cardiovascular Society) and nephrology-based guidelines (Kidney Disease: Improving Global Outcomes [KDIGO]) recommend routine use of RAASi, titrated to a maximum tolerated dose, to improve adverse outcomes in individuals with cardiorenal syndrome.<sup>8–11</sup> In practice, RAASi therapy optimization is often limited and prevented by the development of hyperkalaemia.<sup>5</sup> This presents a medical quandary regarding the provision of lifesaving RAASi treatment in the context of the increased risk of resultant hyperkalaemia.

In the face of hyperkalaemia, RAASi dose reduction or discontinuation are the most common utilized therapeutic options. Submaximal RAASi dosing or discontinuation is associated with worse cardiorenal outcomes and increased mortality,<sup>4,12</sup> and once stopped, treatment is often not reinitiated.<sup>13</sup> The goal must therefore be to maintain treatment with disease-modifying drugs (e.g. RAASi) for as long as possible, an approach supported by ESC (2021), KDIGO (2020, 2021), and UKRA guidelines (2020).<sup>2,3,9,10</sup> In cases where hyperkalaemia is a barrier to guideline-directed medical therapy, the ESC HF guidelines (2021) state that administration of potassium-lowering therapy may enable more individuals to initiate and uptitrate RAASi.<sup>2</sup> Similarly, the KDIGO guidelines for managing diabetes in CKD (2020) and for managing blood pressure

in CKD (2021) also state that hyperkalaemia should be managed using potassium-lowering therapy before considering de-escalation of RAASi therapy.<sup>9,10</sup>

As has been shown, people with cardiorenal disease are particularly at risk of complications or mortality and require coordinated and consistent specialist care, but in practice this is not always how they are managed, and individuals may be treated by both cardiology and nephrology functions separately. The lack of unified guidelines for the management of individuals with cardiorenal disease means that cardiologists and nephrologists may be working to different definitions, thresholds, and with a different approach.

Given the available treatment options that can be employed to enable continuation of RAASi therapy, there is an opportunity to define how to optimally manage hyperkalaemia in those with cardiorenal disease.

## Methods

A steering group (the study authors) of cardiology and nephrology experts (including researchers, clinical trial leads, and those involved in guideline development) in HF and CKD from across Europe and North America convened in August 2021 to discuss hyperkalaemia management in people with cardiorenal disease, including any current challenges and opportunities for improvement. Using a modified Delphi methodology guided by an independent facilitator (Triducive), the group identified four main topics of focus:

- A Risk factors and risk stratification for managing hyperkalaemia in people with cardiorenal disease.
- B Prevention of hyperkalaemia for at-risk individuals with cardiorenal disease.
- C Correction of hyperkalaemia for at-risk individuals with cardiorenal disease with potassium-lowering therapy.
- D Cross-specialty alignment (cardiology and nephrology).

These topics were in turn discussed in greater detail by the group and 39 statements were developed (*Appendix Table A1*). These statements were used to inform an online questionnaire. The questionnaire comprised each statement along with a 4-point Likert scale ('strongly disagree', 'tend to disagree', 'tend to agree', and 'strongly agree') to allow respondents to indicate their corresponding level of agreement. The questionnaire also captured some demographic data to assist further analyses (country, role, and years in role).

The questionnaire was distributed to consultant cardiologists and nephrologists with  $\geq 2$  years' experience in role by an independent third party (Sermo). The identity of the respondents was not known to the steering group. Years in role was defined as either 2–5 years or >5 years, and this was stratified to determine any differences based on level of experience. The steering group agreed that due to the complexity of this topic, only those specialists with  $\geq 2$  years' experience in role would be able to provide sufficiently expert responses. Anticipating the challenges of generating consensus across two specialties, the threshold for consensus was therefore set at two-thirds agreement (i.e. 67%) a priori. Consensus would further be defined as 'high' ( $\geq 67\%$  and  $< 90\%$ ) and 'very high' ( $\geq 90\%$ ).

Completed surveys were anonymously collated and analyzed by the independent facilitator to produce an arithmetic agreement score for each statement. This information was then reviewed by the steering group to determine whether specific recommendations could be made, or further rounds of consensus were required. Survey iterations would be performed until the consensus threshold was achieved; however, due to the levels of agreement received after the first round, the steering group agreed that further rounds were unnecessary.

As this study only requested the opinions of physicians, and no patient-specific data were captured, ethical approval was not sought.

## Results

A total of 520 responses from seven countries in Europe and North America were received in the initial distribution round (Figure 1). Combined, 268 responses were received from cardiologists and 252 from nephrologists.

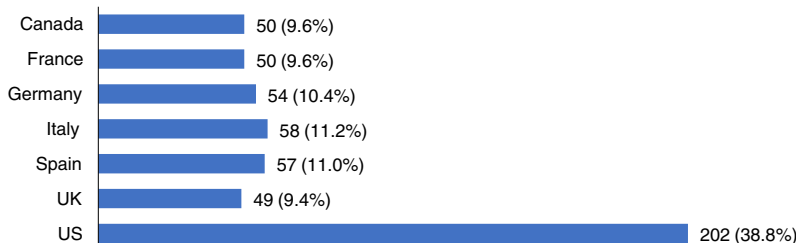
All statements achieved the threshold for consensus agreement (Figure 2); of these, 29/39 statements attained very high agreement ( $\geq 90\%$  agreement) and 10/39 attained high agreement ( $\geq 67\%$  and  $< 90\%$ ).

The alignment between cardiologists and nephrologists was clear, with most statements (32/37) showing a difference of  $\leq 5\%$

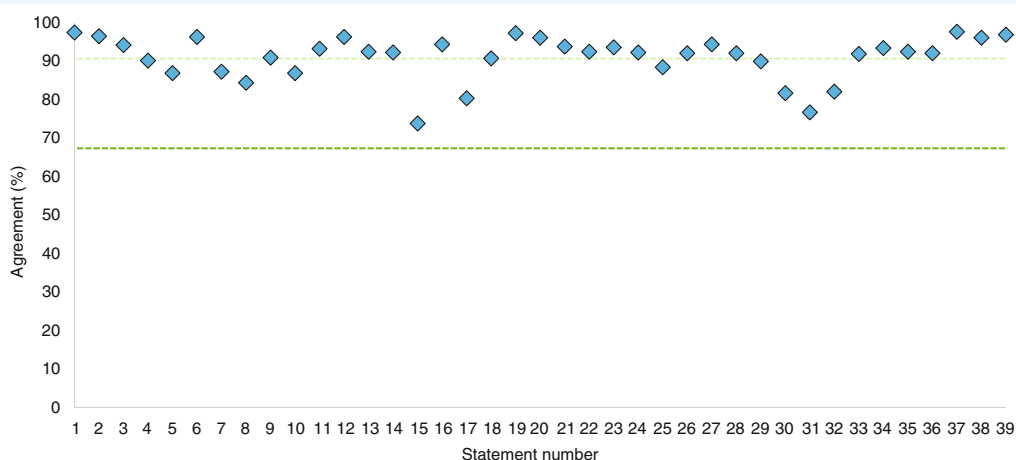
between the two groups (Figure 3). Statement 16 achieved the highest concordance, while statement 31 achieved the lowest, with cardiologists achieving 82% agreement and nephrologists achieving 71%. These low levels of variation suggest that the issues surrounding cardiorenal care are recognized by both specialties with similar perspectives regarding approach to management.

There was clear agreement with all the statements in Topic A (risk factors and risk stratification for managing hyperkalaemia in adults with cardiorenal disease; 8/12 achieving  $\geq 90\%$  agreement; Table 1), demonstrating the recognition from both specialties that hyperkalaemia is a predictable, treatable, and manageable condition in people with cardiorenal disease, and RAASi therapy should be maintained wherever possible to achieve optimal patient outcomes. Notably, there was no significant variation in responses by country or by specialty, suggesting that these are commonly held opinions.

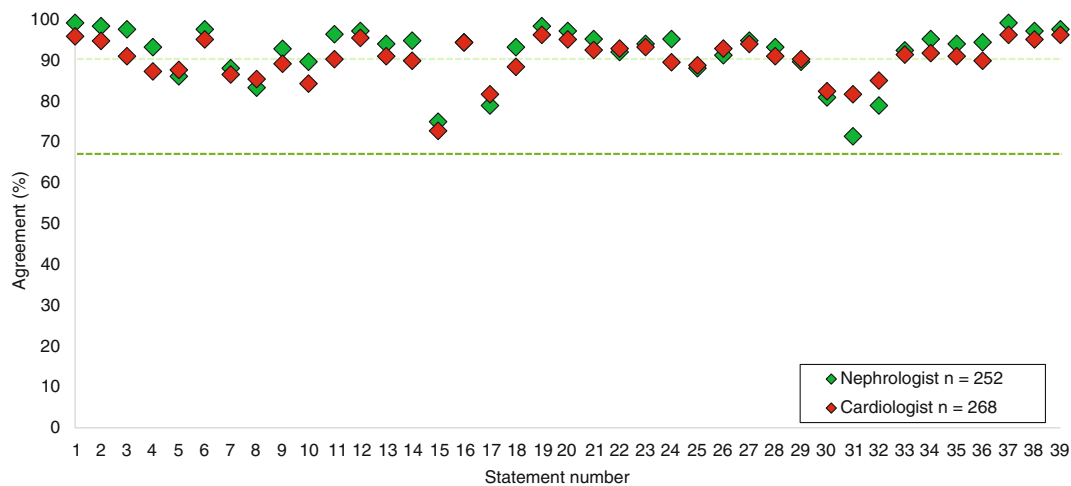
Whilst all statements in Topic B (prevention of hyperkalaemia for at-risk individuals with cardiorenal disease) achieved consensus agreement (5/7 achieving  $\geq 90\%$  agreement; Table 2), statement 15 had a markedly lower agreement level than the others. Variation in response by country is considerable, with the UK and Canada responses being below the agreement threshold.



**Figure 1** Respondent numbers by country (% of total response).



**Figure 2** Combined consensus agreement scores. The dark green line represents consensus threshold of 67% and the light green line represents the threshold for very high consensus (90%).



**Figure 3** Consensus agreement scores by specialty. The dark green line represents consensus threshold of 67% and the light green line represents the threshold for very high consensus (90%). Values for nephrologists and cardiologists overlap at statement 16.

**Table 1** Consensus statements and levels of agreement displayed by country: risk factors and risk stratification for managing hyperkalaemia in cardiorenal patients (Topic A)

No.	Statement	Agreement (%)							
		All	CA	DE	ES	FR	IT	UK	US
1	Optimizing RAASi therapy provides better outcomes for patients	98	98	96	95	92	97	100	100
2	Patients with chronic kidney disease, heart failure, or diabetes are at increased risk of hyperkalaemia	97	96	94	91	94	98	100	98
3	RAASi use is a risk factor for hyperkalaemia	94	100	91	88	94	93	96	96
4	Hyperkalaemia can be effectively managed to optimize disease-modifying therapies, which improve morbidity, mortality, and outcomes	90	92	94	79	86	93	88	93
5	New risk prediction tools are needed if clinicians are to fully individualize risk assessment for their cardiorenal patients	87	92	80	91	86	91	82	87
6	Managing risk of hyperkalaemia should be part of the individualized care plan already in place or planned	96	96	93	93	98	97	96	98
7	There is a need for consistent thresholds for defining and treating hyperkalaemia among sub-specialties	87	90	76	88	94	93	82	88
8	Hyperkalaemia is associated with down-titration or discontinuation of RAASi therapy	84	82	76	88	78	86	94	85
9	When managing mild-to-moderate hyperkalaemia in cardiorenal patients, RAASis should be maintained due to the inherent benefit in this patient type	91	92	89	93	88	86	94	92
10	Mild-to-moderate hyperkalaemia should be managed without de-escalating or discontinuing disease-modifying drugs, such as RAASis	87	88	89	84	92	83	84	88
11	Hyperkalaemia is a known and manageable side effect of RAASi treatment	93	98	96	91	98	88	94	92
12	Hyperkalaemia should be recognized as a predictable, treatable, and manageable side effect of optimal heart failure/chronic kidney disease therapy in patients with a history or at high-risk of hyperkalaemia	96	96	96	89	98	98	96	98

CA, Canada; DE, Germany; ES, Spain; FR, France; IT, Italy; RAASi, renin-angiotensin-aldosterone system inhibitor; UK, United Kingdom; US, United States of America.

**Table 2** Consensus statements and levels of agreement displayed by country: prevention of hyperkalaemia for at-risk cardiorenal patients (Topic B)

No.	Statement	Agreement (%)							
		All	CA	DE	ES	FR	IT	UK	US
13	For high-risk patients currently not hyperkalaemic, preventative measures should be considered (e.g. removal of salt substitutes from diet; and considering diuretics for people with hypertension or some volume expansion)	93	94	87	96	92	90	90	94
14	For those patients who have a known history of hyperkalaemia preventing optimization of RAASi therapy, a novel K <sup>+</sup> binder can be used to enable a trial of RAASi optimization	92	88	91	95	96	86	90	95
15	For high-risk patients currently not hyperkalaemic, the use of a novel K <sup>+</sup> binder can be considered when starting/up-titrating RAASi	74	66	67	74	72	83	49	82
16	Non-disease-modifying therapies that cause hyperkalaemia should be avoided in patients at high-risk of hyperkalaemia, e.g. NSAIDs, amiloride, and herbal supplements	94	94	94	89	94	93	94	97
17	A low K <sup>+</sup> diet is often advised to help manage K <sup>+</sup> levels, with no/little evidence to support, and is counter to a healthy diet that is beneficial to cardiorenal patients	80	80	74	86	74	84	78	82
18	In people for whom dietary restrictions may not be appropriate or desired, the use of novel K <sup>+</sup> binders may enable a balanced diet	91	84	96	91	90	88	90	92
19	People at risk should be monitored closely with a strategy in place to manage K <sup>+</sup> levels effectively	97	96	96	96	96	91	100	100

CA, Canada; DE, Germany; ES, Spain; FR, France; IT, Italy; K<sup>+</sup>, potassium; NSAID; non-steroidal anti-inflammatory drug; RAASi, renin-angiotensin-aldosterone system inhibitor; UK, United Kingdom; US, United States of America.

There were high levels of agreement with the statements in Topic C (correction of hyperkalaemia for at-risk individuals with cardiorenal disease with potassium-lowering therapy; 9/13 achieving  $\geq 90\%$  agreement; Table 3), except for statement 31, which attained consensus overall but with a marked split in response levels by country. Italy, the UK, and the US responses were all  $>80\%$  concordant, whereas Canada, Germany, Spain, and France were all  $<70\%$  concordant.

Responses from all countries demonstrated strong agreement in Topic D (cross-specialty alignment; 7/7 achieving  $\geq 90\%$  agreement; Table 4) with the need for a cross-specialty approach to managing people with cardiorenal disease, supported by consistent guidelines and evidence-based decision making. Strong agreement levels for Topic D suggest that there is a clear case for the implementation of joint clinics to manage those with cardiorenal disease.

## Discussion

### Recommendations

Based on the results obtained, the authors offer the recommendations presented in Table 5.

### Hyperkalaemia and renin-angiotensin-aldosterone system inhibitor use

The management of hyperkalaemia in people with cardiorenal disease is complex and requires a consistent and informed approach. In their responses to this consensus, both cardiologists and nephrologists agree that hyperkalaemia is a predictable, treatable, and manageable condition. Amongst non-specialists or those less experienced in managing hyperkalaemia, a lack of knowledge of current guidelines and treatment options may drive a decision to discontinue or down-titrate RAASi therapy. However, data have shown that although reductions in RAASi treatment may reduce the risk of hyperkalaemia, they are also associated with worsening of the underlying cardiorenal condition and subsequent increase in mortality.<sup>12,14–18</sup>

The results show strong recognition that hyperkalaemia is manageable and when it occurs, treatment optimization to maintain the efficacy of disease-modifying therapies is imperative. In mild-to-moderate hyperkalaemia, RAASi therapy should be maintained without dose reduction as a rule. Individuals with HF and CKD or diabetes should be assessed for risk of hyperkalaemia and an individualized care plan put in place

**Table 3** Consensus statements and levels of agreement displayed by country: correction of hyperkalaemia for at-risk cardiorenal patients with the potassium-lowering therapy (Topic C)

No.	Statement	Agreement (%)							
		All	CA	DE	ES	FR	IT	UK	US
20	A reduction in emergency department visits and unplanned hospitalizations due to complications associated with hyperkalaemia should be a goal of good management	96	96	94	100	94	91	98	97
21	A goal for the management of high-risk cardiorenal patients should be to utilize the maximum recommended dose of RAASi therapy	94	92	89	89	96	88	98	97
22	RAASi-induced hyperkalaemia should not be considered intolerance until other strategies to reduce K <sup>+</sup> have been exhausted	93	92	91	96	94	91	96	91
23	De-escalation or discontinuation of RAASi therapy is associated with worse cardiovascular and renal outcomes in cardiorenal patients	94	92	91	96	94	84	100	95
24	Permanent discontinuation of a RAASi should only be considered as a last resort strategy for chronic hyperkalaemia	92	94	87	88	98	95	96	92
25	Hyperkalaemia should no longer be seen as a barrier to optimization of guideline-directed therapy	88	88	93	91	96	88	82	87
26	Novel K <sup>+</sup> binders enable guideline-recommended RAASi dosing and the proven benefits that this brings to patients	92	90	91	89	90	95	94	93
27	Use of novel K <sup>+</sup> binders in patients with mild hyperkalaemia can enable guideline-recommended doses of RAASi therapy	94	90	93	98	94	100	92	94
28	RAASi use should not be de-escalated or discontinued due to hyperkalaemia unless alternative measures of hyperkalaemia management have been optimized, including initiation of K <sup>+</sup> binder therapy	92	94	94	95	92	91	90	91
29	Novel K <sup>+</sup> binders can enable optimization of RAASi therapy in a similar way that antiemetics can enable optimization of chemotherapy	90	84	89	88	94	93	88	91
30	Novel K <sup>+</sup> binders should not need to show mortality benefit; they enable RAASi, which have an already proven mortality benefit	82	86	74	79	86	86	86	80
31	The use of SPS should be avoided due to concerns with GI toxicity, low compliance due to poor palatability, and is only indicated in severely oliguric or anuric patients	77	60	69	68	66	86	92	82
32	SPS should not be used in the medium- or long-term as it may cause severe GI side effects, including bowel necrosis	82	76	81	75	70	86	90	86

CA, Canada; DE, Germany; ES, Spain; FR, France; GI, gastrointestinal; IT, Italy; K<sup>+</sup>, potassium; RAASi, renin–angiotensin–aldosterone system inhibitor; SPS, sodium polystyrene sulfonate; UK, United Kingdom; US, United States of America.

**Table 4** Consensus statements and levels of agreement displayed by country: cross-specialty alignment (cardiology and nephrology) (Topic D)

No.	Statement	Agreement (%)							
		All	CA	DE	ES	FR	IT	UK	US
33	Patients with cardiorenal comorbidities should be managed by a multidisciplinary team with an agreed management plan	92	92	89	95	88	91	90	94
34	Cross-specialty alignment can enable optimal doses of disease-modifying drugs (RAASi) to be maintained	93	96	93	96	92	93	86	95
35	Cross-specialty management improves patient satisfaction, patient outcomes, and quality of life	93	90	89	86	88	98	96	95
36	Cross-specialty management is a good use of resources and should improve patient outcomes	92	88	96	91	94	97	88	92
37	Enhanced communication between interdisciplinary teams could improve patient outcomes	98	96	98	96	98	95	98	99
38	Cardiology and nephrology guidelines should contain consistent recommendations for the management of hyperkalaemia	96	96	94	96	98	97	92	97
39	Collaborative care and evidence-based decision making (based on guidelines and expert consensus) is an example of best practice and patient centered care	97	98	94	96	98	97	98	97

CA, Canada; DE, Germany; ES, Spain; FR, France; IT, Italy; RAASi, renin-angiotensin-aldosterone system inhibitor; UK, United Kingdom; US, United States of America.

**Table 5** Consensus recommendations for the optimal management of hyperkalaemia in people with cardiorenal disease

#### Recommendations

Based on the results obtained, the authors offer the following recommendations:

- 1 Hyperkalaemia should be recognized as a predictable, treatable, and manageable side effect of optimal heart failure/chronic kidney disease therapy in people with a history or at high-risk of hyperkalaemia.
- 2 RAASi use should not be de-escalated or discontinued due to hyperkalaemia unless alternative measures of hyperkalaemia management have been optimized.
- 3 Novel K<sup>+</sup> binders should be the preferred agent to manage hyperkalaemia, and should be used to enable and maintain optimized RAASi therapy.
- 4 For high-risk individuals that are currently not hyperkalaemic, a thorough history is critical to inform preventative measures.
- 5 Closer cross-specialty collaboration would help optimize outcomes for individuals with cardiorenal disease. Clinical teams should be encouraged and supported to identify suitable methods to achieve this within their care setting.
- 6 Consistent treatment approach should be the goal of new and updated guidelines that support people with cardiorenal disease, and cross-specialty support should be sought for these to ensure aligned clinical practice.

to manage this risk, using universally agreed thresholds for intervention.

There are a range of treatment options recommended for use in managing hyperkalaemia in adults with cardiorenal disease:

- Loop and thiazide diuretics can be used to increase potassium excretion by increasing the delivery of sodium to the collecting ducts. Diuretics are recommended for use in treating mild-to-moderate hyperkalaemia in individuals with adequate renal function.<sup>2</sup> Diuretics also have utility in those with hyperkalaemia and concomitant volume overload or hypertension.<sup>9</sup>
- Oral sodium bicarbonate may be considered in individuals with hyperkalaemia and metabolic acidosis, particularly in those with a serum bicarbonate level of <22 mmol/L, but it is important to consider sodium load, particularly in those at risk of fluid overload.<sup>2</sup> In those at risk of fluid overload, concurrent diuretic use should be considered.<sup>9</sup>
- Two novel potassium binders have recently been developed, patiomer and sodium zirconium cyclosilicate (SZC).<sup>2</sup> Both have demonstrated efficacy,<sup>19–21</sup> and the ESC HF guidelines (2021) and the KDIGO guidelines for managing diabetes in CKD (2020) and for managing blood pressure in CKD (2021) recommend their use for treatment of RAASi-associated hyperkalaemia.<sup>2,9,10</sup>
- Sodium polystyrene sulfonate (SPS) has traditionally been used to treat hyperkalaemia, but there are questions regarding the safety and efficacy of this agent.<sup>22</sup>

Regarding the mixed response to statement 31, the reasons for this variation are unclear but could be due to greater acceptance/experience of SPS in Canada, Germany, Spain, and France. Statement 32 also displayed a similar (though less marked) pattern of variation, although this is perhaps a less refutable statement amongst those specialists that use SPS. People with cardiorenal disease may be on disease-modifying therapy for years with multiple episodes of hyperkalaemia, and due to the questions regarding the safety and efficacy of SPS, novel potassium binders may be the natural choice for managing hyperkalaemia in this population.

Preventative measures should be implemented in those considered to be at high-risk of hyperkalaemia. Cessation of non-disease-modifying therapies that contribute to hyperkalaemia should be implemented where appropriate and diuretics should be considered for those with hypertension or volume expansion. However, an element of caution is recommended as dietary restrictions to reduce the risk of hyperkalaemia have been shown to have limited impact and may deprive the individual of many heart-healthy foods.<sup>23</sup> In individuals at high risk, there is limited clinical trial evidence to support the use of potassium binders as a preventative measure upon RAASi initiation; this may explain the more variable response to statement 15. This variation may also be driven by differences in access to novel potassium binders between individual health economies. For example, the UK health system makes decisions based on the perceived cost-effectiveness of interventions, therefore there may be limited support for 'pre-emptive'

prescribing in the absence of strong evidence of cost-effectiveness. A trial evaluating the use of patiomer to enable treatment with spironolactone in individuals with resistant hypertension and CKD found that patiomer enabled more people to continue treatment with spironolactone, with less hyperkalaemia.<sup>24</sup> A phase 3b trial has recently completed to assess the effects of patiomer compared with placebo on serum potassium in people with HF, and results are expected to be published in 2022.<sup>25</sup> Two clinical trials are currently in progress to evaluate the use of SZC as an adjunct to enable RAASi (a phase 3 trial in CKD and a phase 4 trial in HF).<sup>26,27</sup> The results of these trials should provide insight into the clinical value of this approach in adults with cardiorenal disease.

## Collaborative care and guidelines

Due to the need for both cardiology and nephrology input in the care of individuals with cardiorenal disease, alignment in treatment approach and collaborative care is vital for optimal patient management, and this is recognized by respondents. Individuals with cardiorenal comorbidities should be managed by a multidisciplinary team (MDT) and an agreed management plan put in place. The use of cardio-nephrology MDT meetings to devise a unified management plan may provide several benefits, including improved care outcomes, better utilization of healthcare resources, and increased satisfaction for team members.<sup>28</sup> Modern technology also provides opportunities for closer working through the use of telehealth, virtual meetings, and digital management systems; these should be explored where geographic or logistic barriers to face-to-face working exist.

There is clear support for joint cardiology and nephrology clinics to manage people with cardiorenal disease, but this requires support from both clinicians and wider business functions. If joint/collaborative clinics were adopted, this would improve the impact of support team members, such as physician extenders and nurse practitioners. Findings from the implementation of a cardiorenal clinic in the UK resulted in an increase in the number of individuals on single or dual RAASi, with higher proportions of those being on higher dosages, while having no associated clinically significant deterioration in renal function and hyperkalaemia. As the clinic provided anaemia nurse specialist input and same-day intravenous iron administration, a more efficient use of healthcare resource, minimization of patients' waiting time, transport time, and expense were also identified.<sup>29</sup>

There are initiatives in place to support the cross-specialty approach, including the UK Cardio-Renal-Metabolic (CaReMe) partnership<sup>30</sup> and the Global Multidisciplinary Teams In Cardiometabolic Care Global Program (UNITE).<sup>31</sup> In line with any cross-specialty approach, local and national guidelines should be updated and published.

Regarding guidelines, there are many guidelines covering HF and CKD at both the local, national, and international level, of varying complexity and modernity. Any guidelines for people with cardiorenal disease should ideally be co-created by cardiology and nephrology specialists to reflect best practice and



insights, and to agree on a common approach. This approach supports evidence-based management of hyperkalaemia, and aligns with the implementation of joint clinics and cardiorenal-specific MDTs.

The use of novel potassium binders to manage hyperkalaemia is gaining traction, and recent guidelines from ESC, KDIGO, and the National Institute for Health and Care Excellence reflect this. These guidelines are also well aligned regarding hyperkalaemia management, and could help to close any 'treatment gap' between cardiologists and nephrologists. The agreement levels achieved in this consensus provide further support for this approach. The impetus now is to ensure that local guidelines (country or region specific) are adapted to reflect this.

Whilst the immediate (and understandable) response to hyperkalaemia may be to reduce RAASi dose or stop treatment entirely, healthcare professionals should be aware of the options available to manage hyperkalaemia in people with cardiorenal disease and maintain their outcomes. Novel potassium binders should be considered for hyperkalaemia to enable individuals to access disease-modifying therapies. In terms of benefit, this approach is akin to the use of antiemetics to enable chemotherapy in people with cancer.

## Conclusions

This consensus document is based on expert opinion from 520 cardiologist and nephrologist respondents across five European countries, the US, and Canada. Specialists agree that RAASi therapy should be maintained where possible (certainly for those with mild-to-moderate hyperkalaemia) and novel potassium binders utilized to enable individuals to access the maximal dose of their disease-modifying therapies. This provides an opportunity to manage hyperkalaemia without compromising the therapeutic benefits of RAASi therapy in people with cardiorenal disease. Collaboration between cardiology and nephrology specialties in the treatment of individuals with cardiorenal disease should be formalized (ideally in the form of a cardiorenal MDT), and treatment approach aligned based on evidence-based medicine. The strong agreement levels achieved from many experienced specialists support the collaborative, optimal management of hyperkalaemia in individuals with comorbid cardiorenal disease. A key first step would be for local guideline writers and institutions to adopt a coordinated approach across cardiorenal specialists to review and align local guidance for hyperkalaemia management.

## Strengths and limitations

The large number of experienced cardiology and nephrology specialists that responded to the consensus questionnaire lends weight to the validity of the recommendations proposed by the steering group. Responses were sought from seven countries across Europe and North America, reducing any country-specific bias, although the large number of responses from the US in comparison to other countries will undoubtedly have the greatest influence on results. The clearly defined inclusion criteria ensured

that only the views of experts within their field were sought. The use of a third party to manage the anonymous questionnaire distribution and subsequent collection of results reduces any bias from the steering group.

As this study only undertook one round of consensus with no adjustments to the statements, it is possible that some of the statements were too agreeable and did not sufficiently challenge the status quo. Further research on this question should refine the statements generated herein to determine any greater variance that may exist. Convenience sampling may have introduced motivation bias into the study. However, this was mitigated by seeking responses from across the countries represented by the steering group and by permitting responses at any time during the study period to allow the most reflective response to the statements.

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## Appendix A

**Table A1 Consensus statements**

No.	Statement
<b>A) Risk factors and risk stratification for managing hyperkalaemia in cardiorenal patients</b>	
1	Optimizing RAASi therapy provides better outcomes for patients
2	Patients with chronic kidney disease, heart failure, or diabetes are at increased risk of hyperkalaemia
3	RAASi use is a risk factor for hyperkalaemia
4	Hyperkalaemia can be effectively managed to optimize disease-modifying therapies, which improve morbidity, mortality, and outcomes
5	New risk prediction tools are needed if clinicians are to fully individualize risk assessment for their cardiorenal patients
6	Managing risk of hyperkalaemia should be part of the individualized care plan already in place or planned
7	There is a need for consistent thresholds for defining and treating hyperkalaemia among sub-specialties
8	Hyperkalaemia is associated with down-titration or discontinuation of RAASi therapy
9	When managing mild-to-moderate hyperkalaemia in cardiorenal patients, RAASi should be maintained due to the inherent benefit in this patient type
10	Mild-to-moderate hyperkalaemia should be managed without de-escalating or discontinuing disease-modifying drugs, such as RAASi
11	Hyperkalaemia is a known and manageable side effect of RAASi treatment
12	Hyperkalaemia should be recognized as a predictable, treatable, and manageable side effect of optimal heart failure/chronic kidney disease therapy in patients with a history or at high-risk of hyperkalaemia
<b>B) Prevention of hyperkalaemia for at-risk cardiorenal patients</b>	
13	For high-risk patients currently not hyperkalaemic, preventative measures should be considered (e.g. removal of salt substitutes from diet; and considering diuretics for people with hypertension or some volume expansion)
14	For those patients who have a known history of hyperkalaemia preventing optimization of RAASi therapy, a novel K <sup>+</sup> binder can be used to enable a trial of RAASi optimization
15	For high-risk patients currently not hyperkalaemic, the use of a novel K <sup>+</sup> binder can be considered when starting/up-titrating RAASi
16	Non-disease-modifying therapies that cause hyperkalaemia should be avoided in patients at high-risk of hyperkalaemia, e.g. NSAIDs, amiloride, and herbal supplements
17	A low K <sup>+</sup> diet is often advised to help manage K <sup>+</sup> levels, with no/little evidence to support, and is counter to a healthy diet that is beneficial to cardiorenal patients
18	In people for whom dietary restrictions may not be appropriate or desired, the use of novel K <sup>+</sup> binders may enable a balanced diet
19	People at risk should be monitored closely with a strategy in place to manage K <sup>+</sup> levels effectively
<b>C) Correction of hyperkalaemia for at-risk cardiorenal patients with K<sup>+</sup> lowering therapy</b>	
20	A reduction in emergency department visits and unplanned hospitalizations due to complications associated with hyperkalaemia should be a goal of good management
21	A goal for the management of high-risk cardiorenal patients should be to utilize the maximum recommended dose of RAASi therapy
22	RAASi-induced hyperkalaemia should not be considered intolerance until other strategies to reduce K <sup>+</sup> have been exhausted
23	De-escalation or discontinuation of RAASi therapy is associated with worse cardiovascular and renal outcomes in cardiorenal patients
24	Permanent discontinuation of RAASi therapy should only be considered as a last resort strategy for chronic hyperkalaemia
25	Hyperkalaemia should no longer be seen as a barrier to optimization of guideline-directed therapy
26	Novel K <sup>+</sup> binders enable guideline-recommended RAASi dosing and the proven benefits that this brings to patients
27	Use of novel K <sup>+</sup> binders in patients with mild hyperkalaemia can enable guideline-recommended doses of RAASi therapy
28	RAASi use should not be de-escalated or discontinued due to hyperkalaemia unless alternative measures of hyperkalaemia management have been optimized, including initiation of K <sup>+</sup> binder therapy
29	Novel K <sup>+</sup> binders can enable optimization of RAASi therapy in a similar way that antiemetics can enable optimization of chemotherapy
30	Novel K <sup>+</sup> binders should not need to show mortality benefit; they enable RAASi therapy, which have an already proven mortality benefit
31	The use of SPS should be avoided due to concerns with GI toxicity, low compliance due to poor palatability, and is only indicated in severely oliguric or anuric patients
32	SPS should not be used in the medium- or long-term as it may cause severe GI side effects, including bowel necrosis
<b>D) Cross-specialty alignment (cardiology and nephrology)</b>	
33	Patients with cardiorenal comorbidities should be managed by a multidisciplinary team with an agreed management plan
34	Cross-specialty alignment can enable optimal doses of disease-modifying drugs (RAASi) to be maintained
35	Cross-specialty management improves patient satisfaction, patient outcomes, and quality of life
36	Cross-specialty management is a good use of resources and should improve patient outcomes
37	Enhanced communication between interdisciplinary teams could improve patient outcomes
38	Cardiology and nephrology guidelines should contain consistent recommendations for the management of hyperkalaemia
39	Collaborative care and evidence-based decision making (based on guidelines and expert consensus) is an example of best practice and patient centered care

GI, gastrointestinal; K<sup>+</sup>, potassium; NSAID, non-steroidal anti-inflammatory drug; RAASi, renin-angiotensin-aldosterone system inhibitor; SPS, sodium polystyrene sulfonate.

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